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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/933,115	08/20/2001	Paul B. Fisher	A34466 (070050.1618)	7088

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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/933,115	FISHER, PAUL B.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-11,13,14,16-24,26-31,33,34 and 36-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6-11,13,14,16-24,26-31,33,34 and 36-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 7/26/04. The amendment has been entered. Claims 1, 3, 4, 6-11, 13, 14, 16-24, 26-31, 33, 34 and 36-42 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Election/Restrictions

Claims 10, 21, and 41 have been amended to encompass an invention that is independent and distinct from the invention originally claimed for the following reasons: the instant claims now encompass a method for inhibiting proliferation of cancer cells having a ras gene mutation which increases RAS activity, by increasing the amount of MDA-7 in said cancer cells via administration an effective amount of an **MDA-7 protein** to said cancer cells and also by decreasing RAS activity in said cancer cells via administration of anti-RAS molecule to said cancer cells. (Emphasis added for clarity). As such the claims have now been amended to encompass a method comprising administering an MDA-7 protein to a cell (i.e., protein therapy). Previously, the claims encompassed administering a nucleic acid encoding MDA-7 to a cell (i.e., gene therapy). Protein therapy encompasses a method that is unrelated to a gene therapy method because protein therapy encompasses administrating a protein to a cell, while gene therapy encompasses administering a nucleic acid encoding a therapeutic molecule to a cell. Proteins

and nucleic acids are structurally and functionally different compounds. For instance, proteins are comprised of amino acids and have various functions in cells such as enzymatic functions, as well as cell structural functions in a cell, while nucleic acids are not composed of amino acids and the function of nucleic acids includes encoding sequences that are expressed in cells. As such, the instant claims (as well as dependent claims 26-28) encompass an invention that is non-elected by original presentation. The instant claims are therefore examined only to the extent that the claims read on the originally elected subject matter (increasing MDA-7 in the cell by administering a nucleic acid encoding MDA-7 to the cell) and the non-elected invention is withdrawn from consideration. See 37 CFR 1.142(b) and MPEP § 821.03. It is also pointed out that the original restriction requirement set forth a restriction separating method claims comprising protein therapy from method claims encompassing combination gene therapy.

Claim Objections

Claims 10, 21, and 41 have been amended to encompass an invention that is independent and distinct from the invention originally claimed for the reasons set forth above. Therefore, the claims are objected to for comprising subject matter drawn to a non-elected invention. Correction of the instant claims, for instance, by deleting the non-elected subject matter from the claims would obviate this rejection.

Additionally, claims 22-24 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, claim 22 depends on claim

21 which is drawn to a method for inhibiting proliferation in a population of pancreatic cancer cells having a mutated K-ras gene by administering a nucleic acid encoding MDA-7 protein in expressible form and an anti-RAS agent. Claim 22 is drawn to the method of claim 21 wherein the amount of MDA-7 is increased by introducing into one or more cells of the population a nucleic acid encoding MDA-7 protein in expressible form. Therefore, claim 22 does not further limit claim 21 as no new limitations are set forth in claim 22. Claims 23 and 24 depend on claim 22 and are thus objected to for the same reason.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10, 11, 13, 14, 20-24, 30, 31, 33, 34, 40 and 41 are finally rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reasons of as reiterated below. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims encompass a genus of agents including anti-RAS agents that comprises ribozymes, precursor of triple helix, and agents that inhibit EGFr, RAF, MAPKK, MAPK, PI3K. As such, the claims encompass a genus of inhibitor wherein the genus comprises

possibly thousands if not millions of different species molecules considering every possible anti-RAS agent encompassed by the claims.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164).

The claims encompass a genus of molecules that could include possibly thousands of different species (molecules) considering every molecule that could possibly decrease RAS activity in a cell. It is respectfully pointed out that the indicated genus would encompass molecules which have not yet been identified, as well as molecules having unrelated chemical structures which function through different biological pathways. For instance the genus of molecules would encompass antisense nucleic acid molecules, small organic molecules, polypeptides, hormones, transcription factors, expression inhibitors, etc.

The specification only discloses certain specific molecules that are agents that decrease RAS activity in a cell. The specification only explicitly describes certain molecules that directly inhibit the expression of RAS in a cell. Specifically, the disclosed molecules which can inhibit RAS activity in a cell are ras-specific antisense molecules, dominant-negative RAS inhibitor and farnesyl transferase. It is also acknowledged that one of skill in the art would also recognize ras-specific ribozymes and ras-specific precursor triplex-forming molecules as specific anti-RAS

agents. The specification also discloses dominant-negative RAS inhibitor and farnesyl transferase as inhibitors of RAS activity.

Therefore, although the specification has disclosed a number of specific anti-RAS agents, the disclosure does not meet the standard set in the guidelines in view of the vast breadth of agents encompassed by the claims which specifically includes molecules which are structurally and functionally unrelated to each other. For instance, the claims specifically encompass anti-RAS agents selected from the group consisting of antisense ras molecule, a ribozymes, a precursor of a triple helix and a farnesyl transferase inhibitor. It is noted that the ribozyme and precursor of triple helix are not limited to Ras-specific ribozyme or RAS-specific precursor of triple helix, but includes ribozymes and precursors of triplex that target non-RAS molecules. Also the claims encompass farnesyl transferase inhibitors as well as agents that inhibit EGFr, RAF, MAPKK MAPK and PI3K. As such the claims encompass a genus of inhibitors that includes all possible inhibitors of farnesyl transferase, EGFr, RAF, MAPKK MAPK and PI3K. This includes a huge genus of molecules that includes unidentified molecules as well as molecules that are structurally and functionally distinct. As such, the specification has not disclosed a representative number of species molecules encompassed by the claims.

Additionally, in view of the written description rejection above, claims 10, 11, 13, 14, 20-24, 30, 31, 33, 34, 40 and 41 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As mentioned above, the claims encompass molecules for which there is insufficient written description provided in the specification. Without a clear and adequate disclosure of the species molecules encompassed by the claims, one of skill in the art would not know how to make or use the claimed invention without performing an undue amount of additional experimentation in order to first identify a representative number of species molecules encompassed by the claims.

Response to Arguments

Applicant's arguments filed 7/26/04 have been fully considered and are addressed below.

The Applicants argue that the claims have been amended to more particularly recite molecules that may be used to produce the two desired effects of the present invention, namely increasing the levels of MDA-7 protein and inhibiting RAS activity.

In response, it is acknowledged that the claims have been amended to narrow the scope of molecules that increase MDA-7 protein levels in a cell. Therefore, the rejection, with respect to the inadequate written description of molecules that increase MDA-7 protein levels in cells is withdrawn. However, the amendment has not narrowed the scope of anti-RAS molecules with specific respect to the vast number of ribozymes, precursor triplex forming molecules, etc. as well as the inhibitors of farnesyl transferase and EGFr, RAF, MAPKK MAPK and PI3K. As such, since the instant claims still encompass a vast genus of inhibitors as indicated above, and in view of the limited description of such inhibitors, the rejection of the instant claims is not withdrawn.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 6-11, 13, 14, 16-24, 26-31, 33, 34 and 36-42 are finally rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for inhibiting proliferation and/or inducing apoptosis in cancer cells wherein said cancer cells comprise a mutated ras gene that increases RAS activity in the cancer cell, wherein said method comprises directly administering to said cancer cells a composition comprising:

(i) a nucleic acid that encodes and expresses MDA-7 in said cancer cells, and

(ii) an antisense nucleic acid molecule that specifically hybridizes to a nucleic acid encoding to the mutated ras gene under stringent conditions;

does not reasonably provide enablement for the full scope encompassed by the claims for the reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Response to Arguments

Applicant's arguments filed 7/26/04 have been fully considered and are addressed below.

Applicants argue that the claims have been amended such that the claims are drawn to treating cancer cells containing a mutated ras gene that results in increased RAS activity, which allegedly comports with the disclosed working example which shows a synergistic effect of

MDA-7 and ras antisense molecules in pancreatic cancer cells having a mutation activated ras gene (but not in cells having wild-type ras). Applicants argue that the amended claims capture the functional relationship wherein an increase in RAS activity in the context of malignant cells is addressed by RAS inhibitors in combination with increased levels of MDA-7 protein.

In response, it is acknowledged that the claims have been amended such that the claims are now drawn to treating cancer cells containing a mutated ras gene that results in increased RAS activity. Although the inclusion of this limitation addresses one particular aspect of the rejection of record, the claims still encompass a number of specific problems that have not been overcome by the amendment. Specifically, some claims still encompass a method for "treating" a patient having pancreatic cancer. As previously indicated, the term "treating" is very broad and encompasses not only inhibiting the growth of the pancreatic cancer cells, but also completely curing the pancreatic cancer and also preventing any future occurrence of pancreatic cancer in the subject. The applicants have not specifically addressed the rejection with respect to "treating" pancreatic cancer as it pertains to completely curing and preventing any future occurrence in the patient.

Additionally, the claims encompass inhibiting cancer cell proliferation in a subject by administering compounds to a subject by any route of administration, including systemic administration of the therapeutic compounds. The rejection of record indicates the reasons why the claims are not enabled for the claimed method(s) wherein the therapeutic compounds are administered by any route other than direct administration (i.e., the claims are only enabled for direct delivery of the nucleic acid encoding MDA-7 and the anti-ras agents). Applicants have not rebutted the arguments against non-direct delivery of the therapeutic compounds.

Finally, some claims encompass agents that inhibit farnesyl transferase EGFr, RAF, MAPKK MAPK and PI3K and anti-RAS agents including ribozymes and precursors of triple-helix formations. As indicated above the specification has not adequately described a representative number of these molecules. Furthermore, the claims encompass ribozymes and precursors of triple-helix formations that are not specific to ras, but which do inhibit RAS activity. The only ribozymes and precursors of triple-helix formations that would be able to inhibit RAS activity in a cell that be readily apparent to one of skill in the art would be ribozymes and precursors of triple-helix formations that are specific to the ras gene. To be clear the claims encompass ribozymes and precursors of triple-helix formations that inhibit molecules that in turn then inhibit RAS activity in the cell. Since the specification has not described any ribozymes or precursors of triple-helix formations not targeted to the ras gene that can inhibit RAS activity in a cell, the instant claims are not fully enabled. Applicants argue that the claims have been amended the claims to capture the functional relationship wherein an increase in RAS activity in the context of malignant cells is addressed by RAS inhibitors in combination with increased levels of MDA-7 protein. However, applicants have not specifically rebutted the rejection as it applies to the fact that the claims encompass RAS inhibitors, including ribozymes and precursor triplex formations that are not targeted to the ras gene, but which must inhibit RAS activity in the cell.

Therefore, the claims are finally rejected for not being enabled to the full scope encompassed by the claims for the reasons set forth herein.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon Eric Angell, Ph.D.
Art Unit 1635

DAVE T. NGUYEN
PRIMARY EXAMINER